Letter to the Editor

Association of anti-IgA antibodies with adverse reactions to γ-globulin infusion

To the Editor:

Serum IgG anti-IgA antibody has been associated with the development of adverse reactions (including non-IgE mediated anaphylaxis) to intravenous immunoglobulin (IVIG) in patients with undetectable IgA (here defined as <7 mg/dL).[1] Class-specific anti-IgA antibodies bind both IgA_1 and IgA_2; they are found in 25% to 30% of IgA-deficient individuals, but not in those with IgA >7 mg/dL.[2] Subclass-specific (or limited specificity) anti-IgA reacts with only 1 subclass (IgA_1, $IgA_{2m[1]}$, or $IgA_{2m[2]}$).[2] It is estimated that up to 40% of patients with selective IgA deficiency and 9% to 25% of patients with common variable immunodeficiency (CVID) may have IgG anti-IgA.[3] IgE anti-IgA has been found much less frequently. Three of 4 patients with IgE anti-IgA had anaphylaxis to γ-globulin or other blood products.[4,5]

We conducted a retrospective and prospective observational study to evaluate the possible association with adverse reactions of IgG and/or IgE anti-IgA in IgA-deficient patients receiving IVIG or subcutaneous immunoglobulin (SCIG) at Children's Hospital Boston, Boston, Mass, and Brigham and Women's Hospital, Boston, Mass. All investigations were conducted according to the policies and procedures of the institutional review boards of both institutions.

Among 425 immunodeficient patients receiving IgG therapy, we identified 35 (8.2%) with undetectable IgA; 22 were enrolled. Twenty of these were studied retrospectively (medical record review for 1 year before enrollment) and prospectively (6 months) for symptoms related to IgG infusion. Thirteen patients (11 with CVID, 2 with IgA deficiency) were excluded because of an increase in IgA level (3), lack of consent (7), or nonadherence with the study procedure (3). Blood was collected at enrollment and after the 6-month observation period. Subjects 22 and 23 were studied only prospectively because they did not receive IgG in the year before obtaining the serum specimens. Data were collected with respect to the IgG product, lot number, dose, rate of infusion, use of premedications, and symptoms recorded within 1 hour after the end of the infusion (acute) or up to 72 hours later (delayed). Symptoms were graded as mild (treated by the patients or medical staff without discontinuing the infusion), moderate (requiring telephone contact with, or a visit to an outpatient setting for assistance from, a health care provider, or requiring cessation of the infusion), or severe (requiring an emergency department visit or hospitalization, or resuscitation).

We measured serum levels of IgA_1, IgA_2, and IgG anti-IgA_1 and anti-IgA_2 by ELISA using myeloma controls to establish approximate concentration standard curves. Serum specimens were also studied at the Mayo Clinic Laboratory (Rochester, Minn) by using a Luminex-based assay system and in the Red Cross Laboratory (Philadelphia, Pa) by passive hemagglutination. IgE anti-IgA_1 and anti-IgA_2 were measured by ImmunoCAP assays at ViraCor-IBT Laboratories (Lenexa, Kan).

In all patients throughout the study, only mild symptoms were reported, including headache, fatigue, and malaise. These were of a nature and frequency commonly seen in many clinical trials of IgG therapy that routinely exclude IgA-deficient patients. Therefore, no attempt was made to correlate these symptom data with results of immunoassays.

Results of the immunochemical analyses are shown in Table E1 (see this article's Online Repository at www.jacionline.org). Background levels for IgG anti-IgA_1 or IgA_2 ELISA ranged from 51 to 240 ng/mL (lower limit of assay detection, sera diluted 1:100). Three subjects had levels well above this range (504-4528 ng/mL; Table I). Two individuals (subjects 23 and 32) had class-specific IgG anti-IgA by ELISA. One subject (33) had subclass-specific IgG anti-IgA_2. Subjects 32 and 33 have only ever received SCIG and have never had adverse reactions. Their ability to tolerate IVIG is unknown. Seven years before enrollment, patient 23 had anaphylaxis requiring epinephrine during infusion of an IVIG product containing <10 μg/mL IgA and ceased IgG therapy. The specimen for measurement of IgG anti-IgA was obtained at the time of enrollment in the prospective study, when she began receiving SCIG, which she has now tolerated for 2½ years without any adverse effects. She had a level of IgG anti-IgA (mean of anti-IgA_1 and anti-IgA_2) of 3946 ng/mL. The Mayo Clinic Laboratory reported a total IgG anti-IgA level >1000 arbitrary units, and in the Red Cross Laboratory, IgG anti-IgA was detected. Her IgG anti-IgA level repeated 2½ years later at the Mayo Clinic Laboratory was still >1000 arbitrary units.

The two patients who had class-specific IgG anti-IgA in our assay also tested positive in the Mayo Clinic Laboratory. The 1 individual with subclass-specific IgG anti-IgA_2 did not test positive in the Mayo Clinic Laboratory (result in the "equivocal" range). Subject 23 also tested positive in the Red Cross Laboratory; subject 32 did not. The test was repeated with the same result. The reason for the discrepancy is unknown. The Red Cross Laboratory did detect the subclass-specific IgG anti-IgA_2 that was also found by our ELISA in patient 33. Overall, there is good agreement between our results and these 2 clinical reference laboratories. IgE anti-IgA was not detected in any patient.

Anaphylaxis is very rare among patients receiving IVIG.[6] Therefore, a possible increased risk associated with IgG anti-IgA remains very difficult to quantify. None of the patients evaluated developed a significant reaction during the study period. We could not address the potential clinical significance of the subclass-specific anti-IgA_2 with respect to IVIG, because the only such patient we identified had only ever received SCIG.

Is IgG anti-IgA a "biomarker" of increased risk of non–IgE-mediated anaphylaxis to γ-globulin infusion containing IgA? Several anecdotal reports (including this one) suggest this may be the case. The mechanism whereby anti-IgA antibodies might cause an adverse reaction to IgG that contains some IgA is open to speculation. It has been reported that some individuals react to products with "high" IgA and tolerate products with "low" IgA.[7,8] This could be interpreted as an indication that the reaction mechanism involves interaction of IgG anti-IgA with infused IgA. However, patient 23 appears not to tolerate IVIG products containing even trace amounts of IgA, and some patients with IgG anti-IgA tolerate IVIG without symptoms.[9]

Given the rarity of anaphylaxis to IVIG, much larger prospective studies are required to establish more clearly any possibility of increased risk associated with IgA deficiency. It is not clear that class-specific or subclass-specific IgG anti-IgA antibodies have

TABLE I. Characteristics of patients with positive anti-IgA antibodies

Subject no.	Sex	Age* (y)	Dx, SC/IV†	Spec no.	IgA_1 (ng/mL)	IgA_2 (ng/mL)	CHB IgG anti-IgA_1 (ng/mL)	CHB IgG anti-IgA_2 (ng/mL)	Mayo IgG anti-IgA (AU)‡	RC IgG anti-IgA§
23	F	26	CVID, IV	1	52	20	4528	3363	>1000	Anti-IgA
32	F	60	CVID, SC	1	150	32	2821	1859	684	ND
				2	121	20	4398	3563	>1000	ND
33	M	60	CVID, SC	1	204	116	167	755	172	Anti-IgA_2
				2	253	71	130	504	133	Anti-IgA_2

CHB, Children's Hospital Boston; *Dx*, diagnosis; *F,* female; *M,* male; *Spec*, specimen.
*Age when first serum specimen obtained.
†Therapy at time when serum specimen obtained; *IV,* intravenous infusion; *SC,* subcutaneous infusion.
‡*AU,* Arbitrary units; <100 = negative, 100-200 = equivocal, >200 = positive; maximum result reported >1000.
§Qualitative test, results reported as type of anti-IgA detected, or not detected *(ND)*.

clinical relevance. Our data and others' suggest that further study of a possible association is warranted. In an individual patient, the presence of IgG anti-IgA may indicate a need for closer monitoring, or consideration of alternative therapy such as SCIG, which appears to be tolerated in many of these patients.

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TABLE E1. Results of immunochemical analysis

Subject no.	Sex	Age* (y)	Dx, SC/IV†	Spec no.	IgA_1 (ng/mL)	IgA_2 (ng/mL)	CHB IgG anti-IgA_1 (ng/mL)	CHB IgG anti-IgA_2 (ng/mL)	Mayo IgG anti-IgA (AU)‡	Red Cross IgG anti-IgA§
01	F	8	CID, IV	1	983	1261	127	170	91	ND
				2	824	344	98	164	67	ND
02	F	43	CVID, IV	1	1030	632	60	63	24	ND
				2	445	275	63	68	33	ND
03	F	43	CVID, IV	1	436	220	138	126	84	ND
				2	375	297	170	128	63	ND
04	F	31	CVID, SC	1	185	96			53	ND
				2	550	286	103	92	67	ND
06	F	40	IGAD, IV	1	327	305	129	135	56	ND
				2	318	287	126	155	55	ND
07	F	37	CVID, IV	1	263	159	68	93	45	ND
				2	469	330	241	232	114	ND
08	F	17	CVID, IV	1	459	165	67	93	35	ND
				2	380	150	78	96	48	ND
13	F	15	G4/IGAD, IV	1	342	418	97	164	36	ND
14	M	13	Hypogam, IV	1	343	175	124	108	52	ND
15	M	35	CVID, IV	1	661	232	145	174	73	ND
				2	393	109	59	58	22	ND
18	M	17	CVID, IV	1	245	82	71	81		ND
				2	238	75	87	89	45	ND
19	M	6	Hypogam, IV	1	2473	621	91	100	41	ND
				2	1166	764	118	65	25	ND
20	F	23	CVID, IV	1	236	110	82	106		
				2	225	114	80	93	68	ND
21	F	55	CVID, IV	1	185	59	60	73	57	ND
22	M	6	Hypogam, IV	1	190	53	49	58	14	ND
				2	222	89	74	75	26	ND
23	F	26	CVID, IV	1	52	20	4528	3363	>1000	Anti-IgA
30	F	53	CVID, SC	1	1017	323	115	109	82	ND
				2	773	337	125	115	75	ND
31	M	55	CVID, IV	1	95	4	97	75	54	ND
				2	58	0	75	70	46	ND
32	F	60	CVID, SC	1	150	32	2821	1859	684	ND
				2	121	20	4398	3563	>1000	ND
33	M	60	CVID, SC	1	204	116	167	755	172	Anti-IgA_2
				2	253	71	130	504	133	Anti-IgA_2
34	F	80	CVID, IV	1	130	64	51	98	80	ND
				2	127	47	91	94	77	ND
35	F	29	Hypogam, SC	1	124	84	79	81	65	ND
				2	120	92	63	52	55	ND

CHB, Children's Hospital Boston; *Dx*, diagnosis; *F,* female; *IGAD,* IgA deficiency; *M,* male; *Spec*, specimen.
An empty cell indicates the test was not done.
*Age when first serum specimen obtained.
†*CID,* Combined immunodeficiency; *G2,* IgG_2 deficiency; *G4,* IgG_4 deficiency; *Hypogam,* unspecified hypogammaglobulinemia, consisting of low total IgG level with apparent adequate vaccine antibodies; therapy at time when serum specimen obtained, *IV,* intravenous infusion, *SC,* subcutaneous infusion.
‡*AU,* Arbitrary units; <100 = negative, 100-200 = equivocal, >200 = positive; maximum result reported >1000.
§Qualitative test, results reported as type of anti-IgA detected, or not detected *(ND).*